West-ward
PHARMACEUTICAL CORP.
465 Industrial Way West, Eatontown, NJ 07724
732-542-1678 FAX 732-542-6150

August 13, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

A. ACTION REQUESTED

On August 30, 2001, West-ward Pharmaceutical Corporation ("West-ward") submitted an abbreviated new drug application ("ANDA") for doxycycline hyclate capsules, 20 mg, claiming Periostat® capsules, 20 mg, as the reference listed drug. FDA accepted the application, ANDA 65-103, for filing as of August 31, 2001 by letter dated September 28, 2001. At that time, and to this date, Periostat® capsules have been listed as a reference listed drug in Approved Drug Products with Therapeutic Equivalence Evaluations, or the "Orange Book."

In a Citizen Petition dated July 10, 2002, CollaGenex Pharmaceuticals, Inc. ("CollaGenex") claims that it withdrew its NDA for Periostat® (doxycycline hyclate) 20 mg capsules in September 2001 in accordance with 21 C.F.R. § 314.150(c).[1] In its petition, CollaGenex requests the Commissioner to refuse to approve ANDAs for generic Periostat® capsules: (a) until FDA determines that the drug product was not withdrawn for reasons of safety and effectiveness; and (b) unless the application is accompanied by a petition seeking such a determination as provided under 21 C.F.R. § 314.122. CollaGenex further requests that FDA move Periostat® capsules to the "Discontinued Drug Product List" in the Orange Book and announce the withdrawal of approval of the NDA in the Federal Register as provided by 21 C.F.R. § 314.152, and make these actions retroactively effective to the date the NDA allegedly was withdrawn.

West-ward's ANDA 65-103 was received by FDA and accepted for filing before CollaGenex voluntarily withdrew its NDA. Thus, FDA need not determine that Periostat® was not withdrawn for reasons for safety and effectiveness pursuant to procedures under 21 C.F.R. § 314.122. CollaGenex's request for inclusion of Periostat® capsules on the "Discontinued Drug Product List" in the Orange Book, and its request for an announcement of the withdrawal of

[1] FDA's regulation provides that, "FDA will withdraw approval of an application or abbreviated application if the applicant requests its withdrawal because the drug subject to the application or abbreviated application is no longer being marketed, provided none of the conditions listed in paragraphs (a) and (b) of this section applies to the drug." 21 C.F.R. §314.150(c). (Paragraphs (a) and (b) involve conditions relating to safety and effectiveness .)

02P-0367

CP1

approval of the NDA in the Federal Register, likewise have no bearing on FDA's ability to approve ANDA 65-103 as submitted. The application not only preceded the filing of the CollaGenex petition, it was accepted for filing long before sales of Periostat® capsules by CollaGenex's customers stopped. The sales were made pursuant to prescriptions of dentists to whom CollaGenex promoted the drug.

Nevertheless, in the interest of preventing any delay in the approval of its ANDA, West-ward is submitting this petition under 21 C.F.R. §§ 10.25(a), 10.30, 314.122, and 314.161 to request the Commissioner of Food and Drugs to make a determination that Periostat® capsules were withdrawn for reasons other than safety or effectiveness. Alternatively, if FDA determines that Periostat® 20 mg capsules should continue to be listed as a reference listed drug and/or agrees that this petition is not required under the regulations as discussed above, West-ward requests that FDA promptly deny the CollaGenex petition, as well as dismiss this petition.

B. STATEMENT OF GROUNDS

1. Background

FDA approved NDA 50-744 for Periostat® (doxycycline hyclate USP) capsules, 20 mg, by letter dated September 30, 1998. A copy of the approval letter is attached as **Exhibit A**. CollaGenex began commercially distributing the capsules in November 1998. A copy of a CollaGenex press release announcing the product launch is attached as **Exhibit B**.

CollaGenex submitted NDA 50-783 for a 20 mg tablet formulation of Periostat® dated March 31, 2000. FDA approved NDA 50-783 on February 2, 2001. A copy of the approval letter is attached as **Exhibit C**. CollaGenex launched the tablet formulation of Periostat® in July 2001. A copy of a CollaGenex press release announcing the product launch is attached as **Exhibit D**. In the press release, CollaGenex stated that the tablets "will eventually replace the current capsule formulation."

On August 30, 2001, West-ward submitted an abbreviated new drug application ("ANDA") for doxycycline hyclate capsules, 20 mg, claiming Periostat® capsules, 20 mg, as the reference listed drug. FDA accepted the application for filing as of August 31, 2001 by letter dated September 28, 2001. A copy of FDA's letter is provided as **Exhibit E**. Periostat® capsules were then and continue to be listed as a reference listed drug in Approved Drug Products with Therapeutic Equivalence Evaluations, or the "Orange Book."

West-ward recently learned from a citizen petition submitted by CollaGenex that, by letter dated September 24, 2001, CollaGenex purported to withdraw NDA 50-744 for Periostat® capsules in accordance with 21 C.F.R. § 314.150(c). A copy of CollaGenex's citizen petition is attached as **Exhibit F**. In its withdrawal letter, CollaGenex refers to a prior agreement with the agency "to withdraw NDA 50-477 after the transition from capsules to tablets was complete."

2. Evidence Demonstrating Periostat® Capsules Were Withdrawn for Reasons Other than Safety or Effectiveness

Publicly available documents identify several reasons unrelated to Periostat® safety or effectiveness for CollaGenex's decision to voluntarily withdraw Periostat® capsules from the market:

- NDA 50-744 was approved upon condition that CollaGenex conduct a Phase 4 study or studies. See Exhibit A at 2, which does not disclose the exact nature of all Phase 4 commitments because the pertinent text is redacted. However, it appears that at least one of the commitments, and the principal one at that, was an in vivo food effect study. As noted in the pre-IND/End of Phase II meeting minutes discussing the tablet dosage form and its relationship to the approved capsules, "[t]he protocol as designed will address the impact of food on the Periostat dosage form and thus fulfill the Agency Bipharmaceutic's Phase 4 request for NDA 50-744." **Exhibit G** at 3. The minutes then reflect that "the FDA would release the Sponsor [CollaGenex] from their previous phase IV commitment related to the capsule [provided] the capsule would no longer be in the marketplace." Id.

- The only clinical evaluation of the new tablet dosage form CollaGenex was required to perform was a bioequivalence study to show that the tablets were therapeutically equivalent to the approved capsules pursuant to the draft Food-Effect Bioavailability Bioequivalence Studies Guidance issued October 1997. Id. Indeed, the only apparent reason that the tablets were approved pursuant to an NDA submission was that CollaGenex declined to seek and file the alternative ANDA. It was told by FDA that it could "submit this application as a 505(b)(1) application or submit a suitability petition for this application to be granted ANDA status." Id at 1. It should go without saying that an ANDA suitability petition may not be granted, and FDA would not suggest consideration of one to a new drug sponsor, if the predicate drug was regarded as unsafe or ineffective and the covering application should be withdrawn on safety or lack of effectiveness grounds.

- In a press release announcing the approval of Periostat® tablets, CollaGenex represented that the "tablets can be manufactured at a lower cost than capsules, and we expect to experience improvements in our gross margin after the tablets are launched later this year." A copy of the press release is provided as **Exhibit H**. A press release announcing the launch of Periostat® tablets further explained: "The newly-developed manufacturing method of tablets allows our contract manufacturer to produce substantially larger batch sizes than previously . . . which leads to considerable improvements in manufacturing efficiency. We expect to see the full financial impact of this in the fourth quarter of this year." A copy of the press release is provided as **Exhibit D**. Neither of these releases suggests that CollaGenex had reservations about, or had received notice from FDA concerning, a lack of safety of the capsules. Effectiveness could hardly be an issue in that the two dosage forms are bioequivalent.

- The press release announcing the launch of Periostat® tablets reflects that strategic marketing purposes also motivated the switch from capsules to tablets. In the release, CollaGenex stated: "Many patients find tablets easier to swallow than capsules, and tablets are a much preferred dosage formulation in Europe . . . . One additional benefit of the tablet formulation is that the CollaGenex salesforce will now be able to sample a convenient blister pack to dentists to facilitate trial of Periostat in their patients. Previously, sampling had been limited to the provision of a bottle of 100 capsules, from which the dentist had to dispense samples for patients." See **Exhibit D.**

These documents demonstrate that CollaGenex's decision to withdraw Periostat® capsules was due to economic and strategic marketing reasons.

3. Evidence Demonstrating Periostat® Capsules Were Not Withdrawn for Reasons of Safety or Effectiveness

West-ward has reviewed publicly available documents relating to the approval of NDA 50-744 and 50-583 for Periostat® 20 mg capsules and 20 mg tablets and found no evidence that CollaGenex withdrew its capsules NDA for reasons of safety or effectiveness. These documents show that the currently marketed tablet formulation is, other than in dosage form, essentially identical to the withdrawn capsule formulation, and that the NDA for the tablet formulation referenced the safety and efficacy studies that supported the capsule NDA. FDA's review and evaluation of pharmacology/toxicology data for the tablet formulation states that the "formulations and proposed usage of the two [capsule and tablet] products are identical, with the exception that the tablets contain [redacted] (a film coating agent) in lieu of a hard gelatin capsule." A copy of the review is provided as **Exhibit I**. The only additional studies conducted in support of the NDA for Periostat® tablets were the bioequivalence studies to demonstrate equivalence with the capsules. See FDA's Chemistry Reviews for NDA 50-783 provided as **Exhibit J**.

It stands to reason, therefore, that the capsules could not be withdrawn for reasons of safety or effectiveness without similar issues affecting the currently marketed tablets. There is no indication that the hard gelatin capsule presented any safety or effectiveness issues.

We also note that no recalls or other enforcement action, other than untitled letter issued by the Division of Drug Marketing, Advertising and Communication ("DDMAC") in October 2000 regarding certain advertisements for Periostat®, have been reported for Periostat® capsules.

C. ENVIRONMENTAL IMPACT

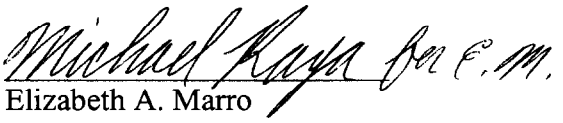
The action requested is categorically excluded under 21 C.F.R. §§ 25.30(a) and 25.31(d) and, therefore, no environmental assessment or environmental impact statement is required.

D. ECONOMIC IMPACT

Economic impact information will be provided if requested by the Commissioner.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



Elizabeth A. Marro
Senior Director
Regulatory Affairs and Quality Assurance
West-ward Pharmaceutical Corporation
465 Industrial Way West
Eatontown, NJ 07724
(732) 542-1678

Of Counsel:

Eugene M. Pfeifer
Elizabeth S. Crockett
King & Spalding
1730 Pennsylvania Avenue, N.W.
Washington, D.C. 20006
(202) 737-0500